The ACCE Model Process:

Steps Leading Up to Its Development

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Preliminary Check-off List for Evaluating a Screening or Diagnostic Test

(Includes both laboratory tests and other approaches, such as questionnaires)

Wald N, Cuckle H. Reporting the assessment of screening and diagnostic tests. *Br J Obstet Gynaecol*, 1989;96:389-396

The Medical Disorder Being Sought

- Is the disorder well defined?
- What is it?
- Is it sufficiently serious in terms of morbidity/mortality to warrant testing?

The Prevalence of the Disorder

- Is the prevalence known in the population being tested?
- What is the prevalence?

The Testing Process

- What is the test (or tests) being used?
- Is it a screening or a diagnostic test?
- Is management of the process centralized?

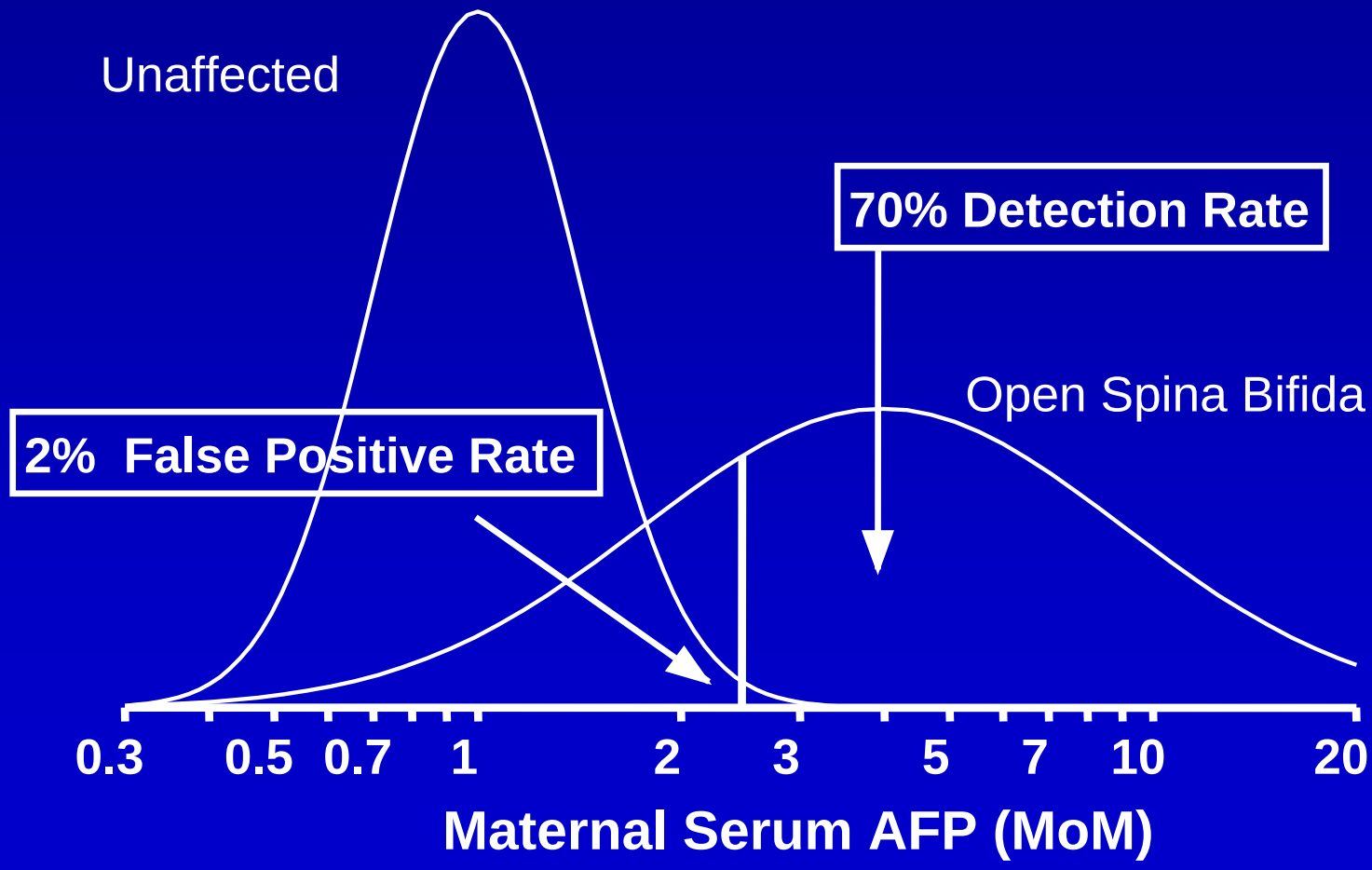
Follow-up Testing and Intervention

- If it is a screening test, what diagnostic test will follow?
- For positive diagnostic tests, what therapeutic intervention will follow?
- What is the efficacy of intervention?

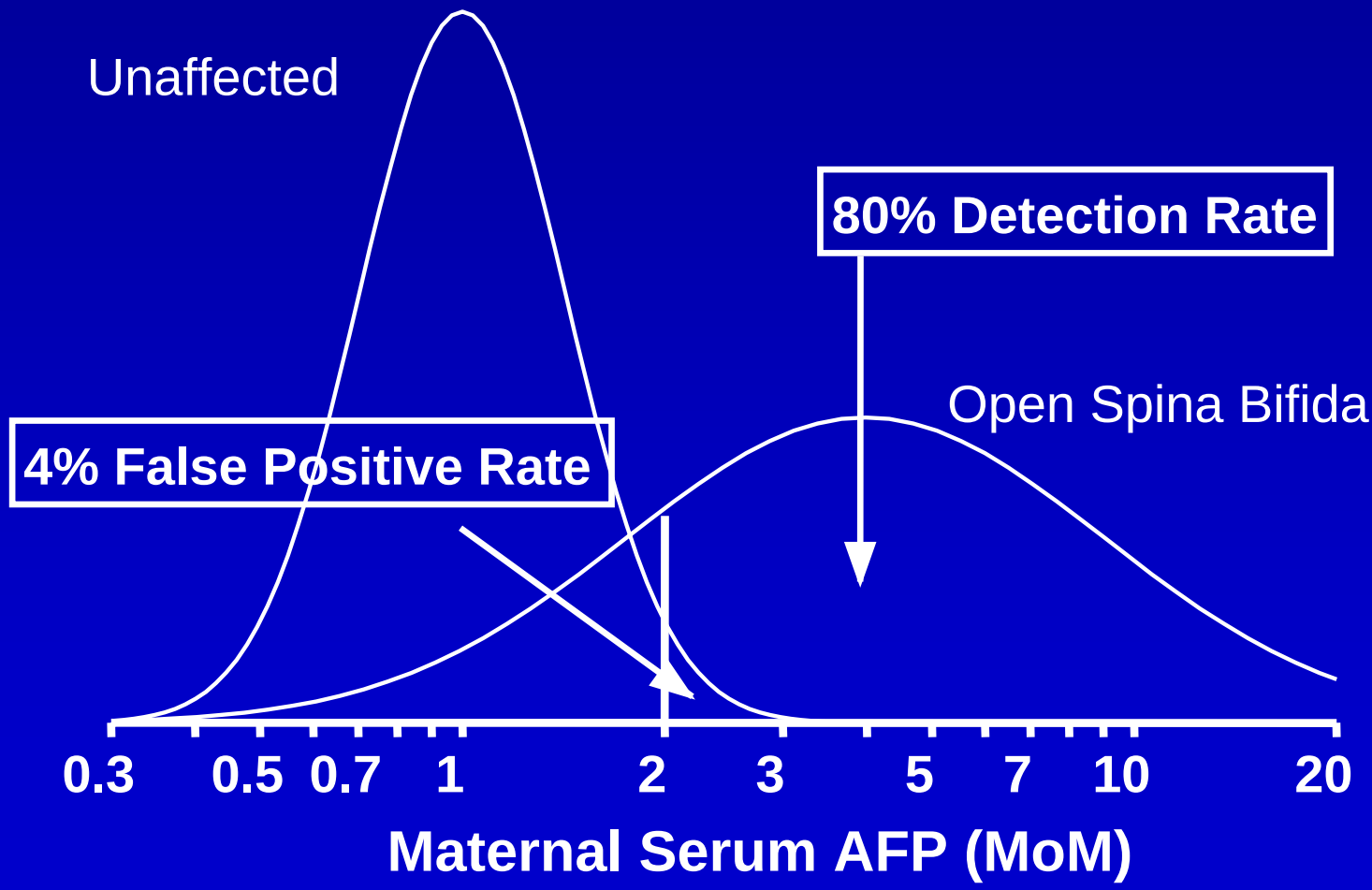
Test Results

- Is the test qualitative or quantitative?
- For quantitative tests, what is the distribution of measurements in affected and unaffected subjects?

Screening for Open Spina Bifida at an AFP Cut-off of 2.5 MoM



Screening for Open Spina Bifida at an AFP Cut-off of 2.0 MoM



Test Performance

- What is:
  - The detection rate?
  - The false positive rate?
  - The odds of being affected, given a positive result?
- Can a flow diagram be constructed, starting with 100,000 individuals, and ending with the final outcome (segregating affected from unaffected, at the outset)?

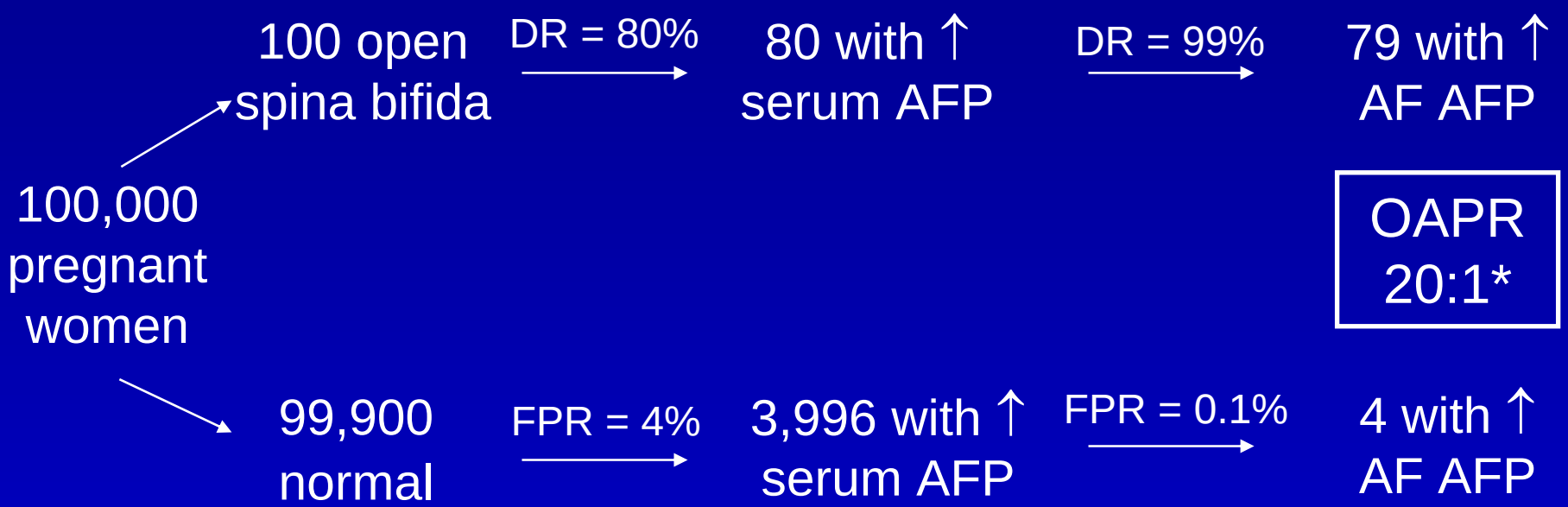
Test Performance: Definitions

High Serum AFP	Open Spina Bifida: Yes	Open Spina Bifida: No
Yes	80	4
No	20	96

Detection Rate = 80 / (80 + 20) = 80%

False Positive Rate = 4 / (4 + 96) = 4%

Test Performance



* If acetylcholinesterase testing is also included, OAPR is much higher

DR = detection rate, FPR = false positive rate, AF = amniotic fluid

OAPR = odds of being affected given a positive result

Costs and Benefits

- What are the medical costs and benefits?
- What are the financial costs and benefits?

Practical Problems

- What are the practical problems in implementation?
- Are special facilities required?
- If so, what is their availability or ease of installation?

Applying the Check-Off List to Prader-Willi Syndrome

A problem presented to the New England Regional Genetics Group (NERGG) in 1995

Stated Problem:

Lack of assurance about manufacturer's quality control of molecular probes used for detection Prader-Willi syndrome

Preliminary discussion leads to conclusion that reagent quality appears satisfactory, but quality control on a lab-by-lab basis is unacceptable.

The Evaluation of Prader-Willi testing shifts to the checklist. The evaluation now begins by focusing on the disorder.

The Medical Disorder Being Sought

Prader-Willi syndrome is well defined and sufficiently serious to warrant consideration of testing

Target Population that Might be Tested for Prader-Willi Syndrome, Using the Molecular Probe

- Individuals clinically diagnosed with Prader-Willi syndrome.
- Infants suspected clinically to have Prader-Willi syndrome.
- Pregnant women having amniocentesis for other purposes.
- Obese children whose parents want testing for Prader-Willi.

Prevalence of Prader-Willi Syndrome in the Four Target Populations

Target Population	Prevalence
Individuals diagnosed with Prader-Willi	100:1
Infants suspected to have Prader-Willi	1:10
Women having routine amniocentesis	1:15,000
All obese children	1:1,000,000

The test being used is a molecular probe for detection of a microdeletion.

It is a diagnostic test.

It can detect 7 out of 10 cases of Prader-Willi syndrome. The other three are caused by uniparental disomy.

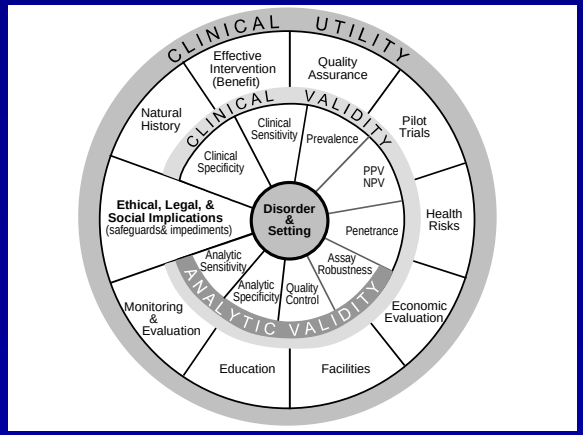
The false positive rate for the microdeletion test is not known but is arbitrarily assigned a rate of 1 per 1000 tests (0.1%)

The prevalence of Prader-Willi in the general population is 1:15,000.

Knowing the detection and false positive rates of the molecular probe, and the prevalence of the disorder, we can now calculate the OAPR (PPV) for the four target populations.

Reliability of a Positive Test Result (microdeletion) for Prader-Willi Syndrome in Four Target Populations

Target Population	Odds that a positive test result is correct (PPV)
Individuals diagnosed with Prader-Willi	1000:1
Infants suspected to have Prader-Willi	70:1
Women having routine amniocentesis	1:21
All obese children	1:1000



ACCE

A CDC-Sponsored Project

AIM: To develop and test a model system to assess the available quantity and usefulness of existing data on DNA-based tests and testing algorithms.

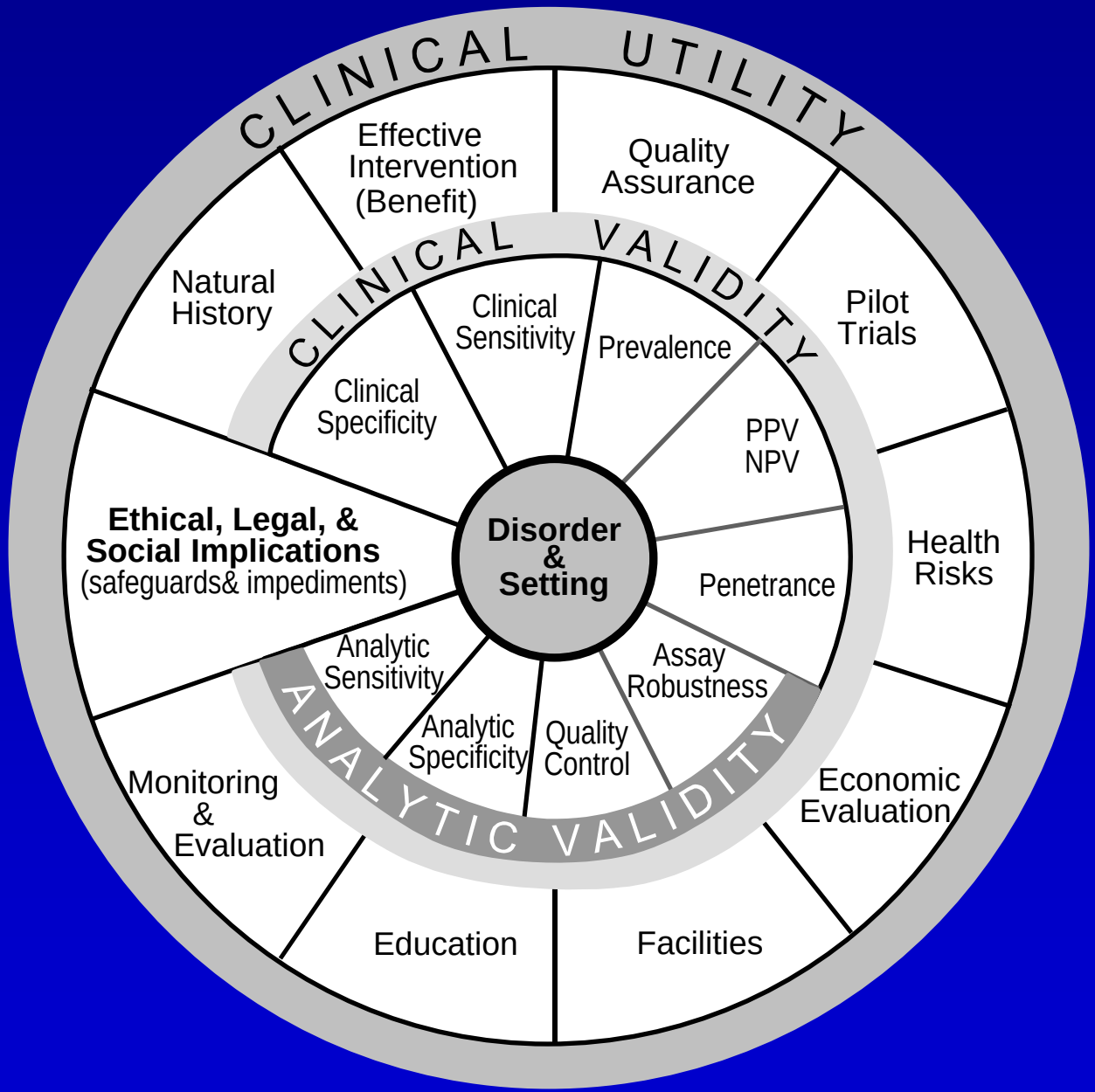
PURPOSE: To provide an up-to-date, accurate and complete summary of available information in forms that are useful to policy-makers, professionals and the general public.

The Model System is Interpreted in Five Steps

- Defining the disorder and setting
- **A** nalytic validity
- **C** linical validity
- **C** linical utility
- **E** thical, legal and social implications

The ACCE project was supported by a cooperative agreement with the CDC, Office of Genomics and Disease Prevention (CCU319352)

The ACCE Model System



These Five Elements are Further Divided into 43 Targeted Questions

Defining the disorder and clinical setting

1. What is the specific clinical disorder to be studied?
2. What are the clinical findings defining this disorder?
3. What is the clinical setting in which the test is performed?
4. What DNA test(s) are associated with this disorder?

ACCE Reviews

- Prenatal Screening for Cystic Fibrosis via *CFTR* Carrier Testing - a full evidence-based review by ACCE core group with expert review
- Screening for Hereditary Hemochromatosis in Adults via *HFE* Mutation Testing - a full evidence-based review by ACCE core group with some input from outside experts
- Testing for Factor V Leiden and Prothrombin Mutations as a Risk Factor for Recurrent Venous Thrombosis in Adults - Full evidence-based review via a collaboration with an external expert group (Dr. Frits Rosendaal, U of Leiden) and FBR staff
- Family History and BRCA1/2 Testing for Identifying Women at Risk for Inherited Breast/Ovarian Cancer - a full evidence-based review by an Epidemiologist with oversight by the ACCE core group and some input from outside experts
- DNA Testing Strategies Aimed at Preventing HNPCC - an ACCE mini-review drafted by an expert (Dr. Peter Rowley, U of Rochester) and revised/edited by the ACCE core group

Issues Identified During the ACCE Review

- The process of identifying, extracting, analyzing, interpreting and reporting published data is time-consuming and best done by individuals trained in epidemiology/statistics with guidance from clinicians
- There is difficulty in summarizing and interpreting data in ways that avoid the appearance of suggesting policy.
- There is a need to distance the process from ‘conventional wisdom’ during the phase of data collection and analysis